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One year change in cognitive function in male and female common
marmosets (*Callithrix jacchus*)

A Thesis Presented

by

BRIANNA HEALEY

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

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Neuroscience & Behavior

One year change in cognitive function in male and female common
marmosets (*Callithrix jacchus*)

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ABSTRACT

ONE YEAR CHANGE IN COGNITIVE FUNCTION IN MALE AND FEMALE COMMON MARMOSETS (*CALLITHRIX JACCHUS*)

MAY 2019

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Long term cognitive studies in humans and nonhuman primates such as macaques are difficult because of their long lifespan. The common marmoset (*Callithrix jacchus*) is a non-human primate who shares with humans many features characteristic of primates, including a complex brain and cognitive function. They also have a short lifespan (~10 years) that makes them a great model in studies of cognitive aging. This study focuses on the rate of decline in cognitive function in male and female marmosets based on performance on reversal learning tasks over 2 years of testing.

We found that marmosets improved their overall performance from Year 1 to Year 2 due to practice effect, but that females exhibited an impairment in reversal learning compared to males in both years. We also found important individual differences, with some monkeys showing decline in Year 2 compared to Year 1 while most monkeys maintained or improved their performance in reversal learning over the two years.

We conclude that (1) cognitive flexibility, as assessed by reversal learning, is impaired in middle-aged female marmosets compared to males, likely due to sex differences in habitual vs. goal-directed behavior, and (2) that reversal learning is a sensitive measure that can capture one year individual changes in cognitive function.

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CHAPTER 1

INTRODUCTION

1.1 Age-related Decline in Cognitive Function

Cognitive function changes significantly with age in humans and begins to decline in adulthood, as early as 30 years old (Salthouse 2009). Most ‘fluid’ cognitive domains decline with age, including working memory, reasoning, episodic memory, and speed of processing. In contrast, experience-based abilities, called crystallized abilities, such as vocabulary, are more resistant to aging and can even improve with age (Lindenberger 2014).

These cognitive changes are associated with multiple brain changes that are measurable at the neuroanatomical, neurochemical, and cellular levels (Raz 1988). Age-related changes in the brain are characterized by significant age-related shrinkage in most brain regions, an increase in cerebral ventricles and sulci, alteration of white matter, and region-specific synaptic loss. There are also marked changes in many neurotransmitter concentration and receptor density.

One aspect of cognitive aging that remains unclear today is whether there are sex differences in the trajectories of age-related cognitive decline.

Few longitudinal studies focusing on sex differences in rate of decline have been conducted. One study reported slower rates of decline in women than men on a tests of verbal meaning (Gerstorf et al. 2011). Other studies reported no sex differences in cognitive decline (Finkel et al. 2003; de Frias et al. 2006; Karlsson et al. 2015; Gerstorf et al. 2006; Ferreira et al. 2014). More recent studies suggest steeper decline in men than in women in multiple domains (Jack et al. 2015; McCarrey et al. 2016), including domains for which men show an advantage at baseline, but very little is known about the

mechanisms underlying these differences. To understand how sex might affect the trajectories of cognitive decline it is important to understand cognitive sex differences at young and older ages.

1.2 Sex Differences in Cognition

Sex differences in cognitive function are well documented in humans (Halpern 2012; Kimura 1992; Hampson 1992). Sex Differences emerge early in life, starting before birth *in utero* (Collaer and Hines 1995) and are present at all ages ranging from puberty to adulthood and old age. Women tend to be better at tasks such as episodic recall, verbal recognition, facial recognition, and semantic fluency. In contrast, males perform better on average at visuospatial tasks (Halpern 2012; Hampson and Kimura 1988).

These differences were originally thought to be confined to the hypothalamus and the result of sex hormone exposure (Levine 1966). Recent studies have shown however that sex differences actually exist in multiple parts of the brain and are caused by a several factors including sex hormones, environment, and genetic influences (Cahill 2006; McCarthy et al. 2012). Despite evidence that some cognitive abilities differ between men and women, it is also well known that men and women's cognitive function overlaps greatly in many cognitive domains and that sex differences are not as widespread as previously thought (Hyde 2005). In addition, sex differences in cognition are highly sensitive to cultural influences in humans (Han and Humphreys, 2016), with gender stereotypes (Miller and Halpern, 2014), educational levels (Gerstorf et al. 2006), and, in some cases, economic status (Rabbitt et al. 1995) increasing some cognitive sex differences while decreasing others (Weber et al. 2014). Therefore, the biological basis

of cognitive sex differences in humans remains a highly controversial debate (Cosgrove et al. 2007; Eckes and Trautner 2000; Cahill 2006).

On the other hand, there is convincing evidence that sex differences are under the influences of sex hormones. Androgens masculinize the brain early in life (i.e., organizational effects), and some of these changes are associated with sex differences in cognitive function (e.g., visuospatial function) later in life (Williams et al. 1997; Hampson 2002, 2018). Most convincing evidence for early influences of sex hormones in humans come from girls with congenital adrenal hyperplasia (CAH) and boys with complete androgen insensitivity syndrome (CAIS). Girls with CAH are exposed to high levels of prenatal androgens due to enzyme deficiencies that result in the lack of production of cortisol. Females with CAH are found to have higher spatial ability than their sisters in childhood, adolescence, and adulthood. In contrast, males with low early androgen levels due to CAIS (lack of functional androgen receptor) are found to have lower spatial ability than controls (Berenbaum 2012, 2016).

Sex hormones also modulate cognitive performance in adulthood (i.e., activational effects). In particular, estradiol exerts activational effects on cognition in women. For example, high estradiol (mid-luteal or ovulatory phases of the cycle) has been shown to improve working and verbal memory, but the pattern is reversed for spatial tasks such as mental rotation (Hausmann et al. 2000; Hampson 2018; Hampson and Kimura 1988). There is also evidence that a single dose of testosterone improves spatial performance in women (Aleman et al. 2004) and transgender males (Gomez-Gil et al. 2008). In young men, there are only a few studies on the effects of testosterone administration on cognitive function, because of the potential risks associated with prostate cancer. One study found no effect of testosterone administration in young men (Young et al. 2010).

Testosterone levels decrease progressively with age in men (Harman et al. 2001), and more abruptly after menopause (51 years old on average) in women (Santoro 2011). Hormone replacement studies in menopausal women and older men have provided inconsistent results with regards effects on cognitive function. In women, the most consistent evidence points to an improvement of verbal memory following estrogen replacement (Henry and Sherwin 2012). Findings of the effects of testosterone administration on cognition in men are more inconsistent with small studies reporting benefits on domains such as working memory (Janowsky et al. 2000; Moffat 2005) but larger studies failing to find any effect on cognitive function (Young et al. 2010; Huang et al. 2016). With regards to sex differences in aging, it is possible that age-related reductions in hormone levels lead to weakened sex differences in cognition.

Only a few studies have investigated whether sex differences are present in older age, and most are cross sectional. In one study among people aged 60-64, Maller et al. (2007), reported that women outperformed men on a test of verbal learning whereas men outperformed women on tests of working memory and simple reaction time. Jorm et al. (2004) used a larger age range and compared the cognitive performance of men and women aged 20 to 64. They found that women outperformed men on a test of verbal memory across ages. Similarly, van Hooren et al. (2007) found that women performed better than men on a word list learning task in people aged 67 to 81 years. A problem common to these three studies is that visuospatial skills were not assessed. Munro et al. (2012) incorporated tests of visuospatial function and reported that women outperformed men on tests of psychomotor speed and verbal learning and memory, whereas men performed better than women on tasks of visuoconstruction and visual perception. Thus, the typical sex differences found in young adults were evident in older people.

In summary, fluid abilities decline significantly with age in humans, but it is unclear whether cognitive sex differences that are observed in young age persist in old age and whether men and women differ in their trajectories of cognitive decline. These are important questions because the mechanisms of age-related cognitive decline may be different for each sex. One way to uncover the biological mechanisms underlying sex differences in age-related cognitive decline while minimizing cultural influences is to study an appropriate animal model.

1.3 Marmoset Model

This study will use the common marmoset (*Callithrix jacchus*) as a non-human primate model for human cognitive aging. Marmosets are New World monkeys that are among the smallest anthropoids (approximately 400 grams). Using the marmoset as a model of human aging provides several advantages over testing humans for this study. First, the use of an animal model provides better experimental control than human studies. Second, the marmoset has a short lifespan, around 10 years on average, although their maximum lifespan can reach 21 years (Nishijima et al. 2012). This means that their rate of decline from old age to geriatric age can be studied longitudinally over a few years. The advantage of studying short-lived primates to advance our understanding of aging has long been recognized (Tardif 2011; Okano et al. 2012).

In terms of neural architecture, they have a large brain relative to their body size and the brain architecture is remarkably similar to that of the human brain. These similarities can be seen in cortical expansion (Chaplin 2013), resting state networks (Belcher 2013), and in neurodegeneration (Carrion and Patterson 2012; Hikishima et al. 2015). Around eight years of age, there is evidence of beta-amyloid plaques developed in the cerebral cortex (Geula and Nagykerly 2002). A recent study also found β -amyloid

deposition as well as hyperphosphorylated Tau, two hallmarks of Alzheimer's disease, in the brain of very old marmosets (Rodriguez-Callejas 2016). Marmosets are able to perform complex cognitive tasks (Spinelli et al. 2004) and therefore are excellent models to examine cognitive functioning. They also have a rich social repertoire, sophisticated vocalizations, and exhibit pair bonding and cooperative care of offspring (Miller 2016), which makes them similar to humans from a social aspect as well.

1.4 Goal of this Experiment

Testing was started in middle-age animals (4-6 years old, equivalent to 40-60 human years) in order to see decline over the rest of their lifetime (9-11 years old). The goal of my experiment was to determine age-related cognitive decline in middle-aged male and female marmosets tested at baseline and one year later.

We assessed changes in Reversal Learning, a test of cognitive flexibility that requires subjects to adapt to changing stimulus/reward contingencies. In the standard test, subjects are presented with two stimuli, one of which is always rewarded (simple discrimination). After learning the association between the stimulus and the reward (as assessed by a specific learning criterion), the stimulus/reward contingencies are reversed (simple reversal): the alternate stimulus is now rewarded, and the previously rewarded stimulus is no longer rewarded. It has been shown that reversal learning involves the same brain regions in both humans (Hornak et al. 2004) and marmosets (Clarke et al. 2008); specifically, the orbitofrontal cortex (OFC) (Dias et al. 1997) and striatum (Jackson et al. 2018). Interestingly, sex differences in reversal learning have been documented in both human children and adults (Overman 2004; Hampson 1992, 2002) with males outperforming females, but it is not known whether these sex differences change with aging.

Very few studies have focused on sex differences in aging nonhuman primates (NHPs). One cross-sectional study in rhesus macaques showed that sex differences in spatial memory present in young age (i.e. better performance in males) were no longer present in old age (Lacreuse et al. 2005). This suggested that males may show greater decline than females in spatial memory, but longitudinal studies are needed to validate this hypothesis. My study is the first to examine changes in cognition as a function of age in monkeys of both sexes. Based on the literature reviewed above, we tested the following hypotheses in monkeys tested at baseline and one year later (1) reversal learning declines with age in marmosets; (2) reversal learning shows a male advantage; (3) despite the initial male advantage, the slope of decline is steeper in males than in females.

CHAPTER 2

METHODS

2.1 Subjects

We tested 22 monkeys at baseline, with a subset of 18 monkeys, 9 males and 9 females, completing the second year of tests by the time data collection was terminated for this study. All subjects were middle-aged, between 3.96 – 5.56 years old during year 1 and 5.33 – 7.4 years old in year 2 (See **Table 1**). They were housed in opposite-sex pairs in a room with a 12 h: 12 h dark/light cycle. They were fed a daily diet of fresh food including fruits, vegetables, nuts and seeds, various breads, and ZuPreem marmoset food. During testing days, they were food and water restricted for at least 1 hour before testing and for a maximum of 5 hours in a day. They were given a variety of enrichment at the end of each day after testing as well. Enrichment activities included toys such as red 4-inch plastic balls with holes with pieces of grapes cut up into bite size pieces and hung from the wall of the cage so the marmosets can reach in through the holes to retrieve the grapes. Other forms of enrichment included mealworms, dried fruits, and nuts in the bottom of a metal food dish or plastic rectangular tray, which will then be covered in pine shaving bedding for the marmosets to forage through. The animals were cared for in accordance with the guidelines of the US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals, and the Guide for the Care and Use of Laboratory Animals (2011), 8th edition. The studies were approved by the University of Massachusetts Institutional Animal Care and Use Committee.

2.2 Equipment

The monkeys were tested using the Cambridge Neuropsychological Test Automated Battery (CANTAB) system (see **Figure 1**). The CANTAB machine is a touch-sensitive screen device with a metal tube running down the center of the screen to deliver banana milkshake (unsweetened coconut milk and banana flavored Nesquik) reward. The monkeys were trained to use the touch screen before this experiment. This machine is wirelessly connected to a PC which is used to load and control programs from an adjacent room. The monkeys voluntarily enter a $34.1 \times 20.65 \times 30.8$ cm transport box that attaches to their home cage. The transport box is made of Plexiglas with a steel door on one side and a steel grating on the opposite end for the monkey to reach the milkshake tube and touch screen (see **Figure 2**). The CANTAB is positioned so that the monkey can easily reach through the grating to touch the screen and retrieve the milkshake. The experimenter leaves the room during testing so there are no distractions for the monkey during the test.

Some monkeys had difficulty acclimating to the touch-screen of the CANTAB, so they were tested on the same task but with physical objects in a WGTA (Wisconsin General Testing Apparatus) box instead. The WGTA consisted of an opaque box ($43.2 \times 42.3 \times 44.5$ cm) containing a test tray ($40.65 \times 11.15 \times 1.25$ cm) with two food wells (each of diameter 2.5 cm; **Figure 3**). The wells could be baited with mini-dried marshmallows and covered by stimulus objects. Between trials, the tray was concealed from view by an opaque screen. The stimuli for the WGTA version were made of foamy material of the same shape and colors as the stimuli shown in **Figure 4**. Each stimulus ($2 \text{ cm} \times 2 \text{ cm} \times 0.9 \text{ cm}$) was glued on a 3.5 cm diameter wooden token that completely covered a food well.

2.3 Procedure

Monkeys were previously trained by successive approximations to touch the screen and obtain a milkshake reward following the training protocol described in Spinelli (2004). To enhance participation, prior to testing, food and water was withheld for a minimum of 1 hour and a maximum of 5 hours. Each marmoset was tested daily, five days a week. The tasks they performed were simple discriminations and simple reversals from the Reversal Learning task of the CANTAB to measure their cognitive flexibility. As can be seen in **Figure 4**, they started with simple discrimination 1 (SD1) in which they were presented with a blue triangle and a white line on the screen. For half the monkeys, the blue triangle was rewarded, for the other half, the white line was rewarded. Touching the positive stimulus resulted in a milkshake reward and positive bell sound, and touching the other stimulus resulted in no reward and a negative buzzer sound. Each monkey performed forty trials per day they answered correctly on 36 trials in a total of 40 trials, or 90% correct.

Once they reached criterion on SD1 they moved on to simple reversal 1 (SR1). In SR trials they will be presented with the same two stimuli as the previous SD trial but the correct stimulus was reversed. Once they reached learning criterion on SR1 they moved on to the second round of simple discrimination, or SD2, which were more difficult to discriminate, either two white lines or two pink shapes. They are more difficult because the two shapes in SD2/SD3 are more similar to each other than the shapes in SD1, making them harder to distinguish from one another. They completed each test until 90% correct criterion until SR3, totaling six tasks (SD1, SR1, SD2, SR2, SD3, SR3). In year 2, the stimuli were changed to minimize the effect of repeated testing on performance.

The WGTA procedure was similar to the CANTAB procedure, but with important differences constrained by the WGTA setting. First, trials were given by an experimenter sitting behind the WGTA across the monkey and only 20 trials per day were given to minimize satiety effects; for each trial, the experimenter followed a 20-trial test sheet indicating the location (left or right, randomized) of the rewarded stimulus. With the door closed, the experimenter baited one of the wells with a mini-dried marshmallow and covered it with the positive (reward) stimulus, while the other well was baited with the other (negative) stimulus. The experimenter lifted the door while starting a timer to let the monkey select one of the stimuli. For each trial, the experimenter recorded the performance of each monkey (coded as 0 for incorrect or 1 for correct) as well as the response times (elapsed time between door opening and monkey response) on the test sheet. The monkey had a maximum of 2 minutes to give a response at each trial. A lack of response was recorded as a refusal and the next trial was administered.

2.4 Data Collection

The CANTAB software records which trials the monkey completed successfully, the latency to select a stimulus, and if the monkey refused to respond (refusals). At the end of testing each day, the data stored in the CANTAB were transferred to a desktop computer and converted into Excel files for analysis. These logs were updated daily to see if a monkey had reached criterion so they could proceed to the next testing period. The WGTA data were recorded by the experimenter and also included the number of correct trials, latency to select a stimulus, and any refusals. The data were recorded into an excel file for analysis as well as a daily log to see if a monkey had reached criterion.

CHAPTER 3

RESULTS YEAR 1

3.1 Statistical Analyses

The TTC, and refusals for CANTAB tests were analyzed using a mixed ANOVA with Sex, Pair Number (Pair 1, Pair 2, Pair 3), and Test Type (SD, SR) as factors. The order of presentation of Pairs 2 and 3 (white lines or pink shapes first) was entered as a covariate in the analyses.

3.2 Trials to Criterion (TTC)

The ANOVA revealed a significant main effect of Test Type ($F(1, 19) = 64.86, p < .001$, partial $\eta^2 = .77$) on TTC, with animals taking significantly more trials to learn the SRs ($m = 448.93$, $SEM = 37.51$) than the SDs ($m = 224.24$, $SEM = 22.20$). Additionally, Pair Number was also significant ($F(2, 38) = 21.15, p < .001$, partial $\eta^2 = .53$) with animals taking significantly fewer trials on the 1st pair ($m = 159.37$, $SEM = 15.48$) than on the 2nd ($m = 386.48$, $SEM = 36.88$) and 3rd ($m = 663.91$, $SEM = 50.01$). The main effect of Sex on TTC was not significant ($F(1, 19) = .40, p = .54$, partial $\eta^2 = .02$), however, a significant interaction between Sex and Test Type ($F(1, 19) = 7.93, p = .01$) revealed that females needed more trials ($m = 496.66$, $SEM = 53.17$) than males ($m = 401.22$, $SEM = 53.17$) to reach criterion on the SRs, but not on the SDs (Males: $m = 235.16$, $SEM = 31.46$, Females: $m = 213.33$, $SEM = 31.46$). A significant interaction between Test Type and Pair Number ($F(1.26, 23.88) = 7.12, p = .009$, partial $\eta^2 = .27$) also indicated that monkeys had higher TTC for SRs than SDs on all three pairs (all p 's $< .001$). Finally, a marginal Sex X Test Type X Pair Number ($F(1.26, 23.88) = 3.00, p = .088$, partial $\eta^2 = .14$) suggested that females were especially impaired for the more complex pairs (see **Figure 5**).

CHAPTER 4

COGNITIVE CHANGE YEAR 1 TO YEAR 2

4.1 Statistical Analysis

The average TTC was not significantly different between CANTAB ($M = 254.33$, $SEM = 23.83$) and WGTA monkeys ($M = 215.71$, $SEM = 47.29$, $t(16) = 0.59$, ns), therefore the data of the 18 monkeys were combined for the analysis. However, for the WGTA group of monkeys, the percentage of refusals was much lower (16 %, $SEM = 8.6$) than for the CANTAB monkeys (37.6 %, $SEM = 2.7$). Because of this, the analysis for this variable was performed only on the 16 CANTAB monkeys. The TTC and the percentage of refusals were analyzed using mixed repeated measure ANOVAs with Year (1, 2), Test Type (SD, SR) and Pair Number (Pair 1, Pair 2, Pair 3) as within-subject factors and Sex as a between-subject factor. Initially, the age in Year 1 and time intervals between individual monkey's test start dates were included as covariates in the models. None of the covariates were significant, however, so they were omitted from the final models.

4.2 Trials to Criterion (TTC)

The ANOVA revealed a significant effect of Year ($F(1, 16) = 7.99$, $p = .012$, partial $\eta^2 = .33$) on TTC, with animals taking significantly less trials to perform the discriminations in Year 2 ($m = 207.037$, $SEM = 24.87$) than in Year 1 ($M = 293.04$, $SEM = 25.67$). Test Type was also significant ($F(1, 16) = 89.81$, $p = .0001$, partial $\eta^2 = .85$), which indicates that monkeys took more time to learn the SR tests ($M = 335.06$, $SEM = 27.95$) than the SD tests ($m = 165.02$, $SEM = 13.96$), and the Year did not affect this. Additionally, the monkeys took longer (more TTC) on the 2nd ($M = 270.32$, $SEM = 26.34$) and 3rd ($M = 312.29$, $SEM = 33.95$) pairs as opposed to the 1st pair ($M = 167.51$,

SEM = 12.45). Therefore, TTC also varied according to Pair Number ($F(2, 32) = 14.24$, $p = .001$, partial $\eta^2 = .47$; **Figure 6**). Overall, the main effect of Sex on TTC was not significant ($F(1, 16) = 3.57$, $p = .077$, partial $\eta^2 = .18$). There was, however, a significant interaction between Sex and test Type ($F(1,16) = 4.89$, $p = .042$, partial $\eta^2 = .23$). This interaction shows that females require more TTC ($M = 398.96$, $SEM = 39.52$) than males ($M = 271.17$, $SEM = 39.52$) to complete the SR tests, but there was no sex differences on the SD tests (M males = 152.68, $SEM = 19.74$; M females = 177.35, $SEM = 19.74$; **Figure 6**). As an example, **Figure 7** represents the performance (number of correct responses) of females and males in SR3 as a function of sessions of 40 trials. Males reach criterion (90% correct or 36/40) much earlier than females (session 19). Interestingly, females continue performing at about 75% correct for another 10 sessions before reaching criterion at session 41. Another significant interaction between Year and test Type ($F(1,16) = 4.89$, $p = .042$, partial $\eta^2 = .23$) revealed that the performance improved significantly from Year 1 to Year 2 for the SR tests ($F(1,16) = 7.98$, $p = .012$) but not for the SD tests ($F(1,16) = 0.87$, ns). Other interactions between Pair Number and test Type ($F(2, 16) = 4.84$, $p = 0.15$, partial $\eta^2 = .23$) as well as Pair Number and Year ($F(2, 16) = 11.60$, $p = .001$, partial $\eta^2 = .42$) indicated differences in pair complexity, with pairs 2 and 3 being more difficult. A marginal Sex X Test Type X Pair Number ($F(2,32) = 2.86$, $p = .072$, partial $\eta^2 = .15$) also suggested that females were more impaired for the more complex pairs as opposed to males.

There was a lot of variation in amount of time it took for individual monkeys to reach criterion on the SD tests, which influenced their individual performance on the SR tests as well. To account for these individual differences, we computed a Reversal Index

(RI) (Rajalakshmi and Jeeves 1965) for each year of testing, as follow: $RI = \text{mean} (TTC_{SR1} + TTC_{SR2} + TTC_{SR3}) / \text{mean} (TTC_{SD1} + TTC_{SD2} + TTC_{SD3})$.

The RI takes into account the TTC required for each of the 3 SR tests compared to the 3 SD tests by examining how many more trials were needed on the SR tests. Higher values mean poorer performance. A repeated measure ANOVA with Sex and Year as independent variables showed no significant variations between Years of testing ($F(1, 16) = .035$, ns). Therefore, despite the decrease in TTC from Year 1 to Year 2 which would indicate improved performance, the performance on the SR tests relative to the SD tests did not change from Year 1 to Year 2. In addition to this, the RI for females ($M = 2.31$, $SEM = 0.14$) was significantly higher than the RI for males ($M = 1.84$, $SEM = 0.14$; $F(1, 16) = 5.77$, $p < .05$). This difference indicates that females had poorer performance in both Year 1 and 2, although there was no significance in the interaction between Year and Sex ($F(1, 16) = .45$, ns).

4.3 Refusals

The WGTA data ($n=2$) were excluded from this analysis, and the remaining data ($n=16$) showed that the marmosets tested on the CANTAB refused a large percentage of trials (37.6%). Sex differences existed in the number of refusals, with males ($M = 43.7\%$, $SEM = 3.3$) refusing significantly more trials than females ($M = 31.5\%$, $SEM = 3.3$; $F(1, 14) = 8.47$, $p = .011$, $\text{partial } \eta^2 = .38$), however this differences was dependent on test Type ($F(1, 14) = 4.89$, $p = .044$).

Figure 8 shows that the sex difference was specific to the reversals ($F(1, 14) = 12.02$, $p = .004$), but there was no significant difference noted for the simple discriminations ($F(1, 14) = 2.20$, ns). The main effect of Year ($F(1, 16) = 0.89$, ns) and the interactions were not significant. There was no correlation between the TTC and the

% of refusals ($r(16) = -0.16$, $p = .55$), even after controlling for sex ($r(13) = .11$, $p = 0.70$).

4.4 Individual Trajectories

Individual trajectories were also examined. **Figure 9** shows the individual RIs between the two years of testing. Most marmosets' performance improved from Y1 to Y2 (as shown by a decreased RI), however a few marmosets' performance ($n = 8$) actually worsened (as shown by an increased RI). We speculate that these individuals may follow a trajectory of pathological aging that we will be able to confirm in the subsequent years of testing. Age was not significantly correlated with the change in RI from Y1 to Y2 ($r = -0.22$, $p = .38$). Among these subjects, 4 were males and 4 were females, therefore no obvious sex difference could be detected in cognitive change from Y1 to Y2.

CHAPTER 5

DISCUSSION

This goal of this experiment was to examine the effects of age and sex on cognitive flexibility based on performance on a reversal learning task, in monkeys tested on a CANTAB touchscreen system (n=16) or a manual system, WGTA (n=2). By analyzing data for TTC, refusals, and individual results between Year 1 and Year 2 we are able to draw a few conclusions. First, practice effects for were important, as TTC in Year 2 was significantly lower than in Y1 (**Figures 6 & 8**). Secondly, we did see differences in performance between the sexes in both years, which confirms the importance of sex as a variable in cognition studies.

5.1 Age Effects

We saw little decline in performance when comparing results from Year 1 to Year 2. Despite changing the stimuli between Year 1 and Year 2, practice effects were important, as shown by better TTC overall in Year 2 than in Year 1. Practice effects are often seen in longitudinal studies (Salthouse 2009). One way to overcome these effects is to look at individual trajectories. Most monkeys improved or maintained their performance between the two years of testing. However, 6 of the 18 monkeys did show worsened performance. Further data points will be needed to confirm these data, but current data suggests that some monkeys may follow a trajectory of pathological aging that may be captured by assessing cognitive flexibility.

Interestingly, although performance improved overall, as indicated by the TTC, the RI remained stable across the 2 years. This indicated that the ability to perform a reversal, relative to a simple discrimination remains unchanged, with about twice as many trials required to perform a reversals compared to a pre-reversal performance.

5.2 Sex Effects

We found no difference in performance between males and females on SD tests in either Year 1 or Year 2, but a sex difference was demonstrated for the SR in both years, with females showing impaired performance. especially on the more complex pairs 2 and 3.

Two brain regions seem to be critical to reversal learning, the OFC and the striatum (Izquierdo et al. 2017). Functional imaging studies in humans have shown increased activation in the OFC during reversal learning paradigms (Cools et al. 2002; Ghahremani et al. 2010; Nagahama et al., 2001) and studies in NHPs have shown that lesions to the OFC cause disruptions in reversal, but not in the initial stimulus-reward associations (Izquierdo 2004; Machado & Bachevalier 2007). In addition to the OFC, the striatum, which receives strong projections from the OFC, significantly contributes to reversal learning. For example, lesions of the medial striatum (Clarke et al. 2008) or dopaminergic depletion within the caudate (Clarke 2011) cause impairments in reversal learning in the marmoset. Furthermore, a recent study found that infusion of the GABA A agonist muscimol into the putamen led to impairments in reversal acquisition, while leaving the simple discrimination unchanged (Jackson et al. 2018).

Based on these findings, it is likely that the observed sex difference, specific to reversal acquisition, reflects a sex difference at the OFC/striatum level. The OFC has been implicated in the encoding of the associative value of a reward and is critical for updating this value for future decisions (Haber and Knutson, 2010). In contrast, the dorsal striatum mediates the acquisition and expression of habitual behavior, when the stimulus-responses associations become automatized and less sensitive to the outcome of the response (Graybiel and Grafton, 2015; Fernandez-Ruiz et al. 2001; Miyachi et al, 1997,

2002). Interestingly, this region of the striatum is also highly sensitive to estrogens (Di Paolo et al. 1985; Shams et al. 2016; Korol 2004). In a prior study, we reported that estradiol (E2) replacement impairs reversal acquisition in ovariectomized female marmosets (Lacreuse et al. 2014), consistent with a detrimental effect of E2 on the dopaminergic striatal system. Interestingly, a recent study demonstrated that female rats engage in habitual behavior more rapidly than male rats in an operant responding task (Schoenberg et al. 2018). Based on these findings and the literature reviewed above, one interpretation of our findings is that female marmosets may engage in habitual behavior earlier and/or to a greater extent than male marmosets while learning stimulus-response contingencies, which would impair their ability to flexibly respond to new contingencies as a reversal is implemented. The female impairment is most likely driven by detrimental effects of estrogens on the striatal dopaminergic system. Accordingly, one would expect reversal learning performance to vary with cycling endogenous E2 levels in female marmosets, as found for other striatal-dependent tasks in rodents (e.g., Becker et al. 1987). The specific mechanisms underlying these effects will have to be determined in future studies.

CHAPTER 6

CONCLUSION

This work is the first longitudinal study of cognitive performance in male and female marmosets. Focusing on reversal learning of a set of 3 pairs of stimuli, I have shown that females take longer than males to acquire the reversals, relative to initial discriminations and that the sex difference is apparent across 2 years of testing. We speculate that this impairment may reflect an effect of estrogens on the striatal system, which could bias female performance towards habitual behavior, as opposed to goal directed behavior. Contrary to my hypothesis, monkeys improved from Year 1 to Year 2 of testing due to repeated testing and males and females improved to the same extent. Inspection of individual data indicate that although most individuals maintained or improved their performance from Year 1 to year 2, a subset of monkeys exhibited worse performance in Year 2. We speculate that these individuals may follow a trajectory of pathological aging. As the Lacreuse lab continues testing the monkeys for another year of testing, it will be interesting to see whether these individual trends persist and are associated with increased brain aging.

Table 1. Marmoset Sex and Age In Year 1 and Year 2			
Animal ID	Sex	Age Y1	Age Y2
1	M	3.96	5.33
2	M	4.64	N/A
3	M	4.65	5.79
4	M	4.69	6.37
5	M	4.77	5.84
6	M	5.01	6.43
7	M	5.03	N/A
8	M	5.21	6.43
9	M	5.21	6.88
10	M	5.52	N/A
11	M	5.56	7.4
12	F	4.08	5.38
13	F	4.12	5.81
14	F	4.21	5.45
15	F	4.41	5.49
16	F	4.52	6.31
17	F	4.55	N/A
18	F	4.82	6.48
19	F	4.93	6.19
20	F	4.99	N/A
21	F	5.32	N/A
22	F	6.05	N/A

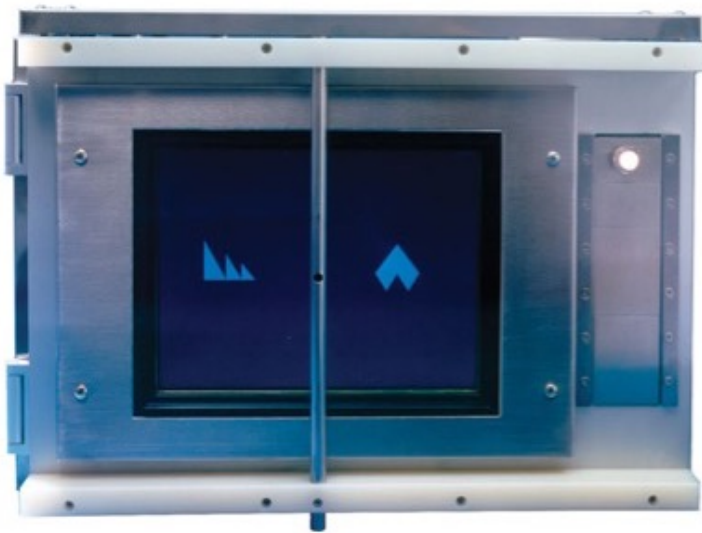


Figure 1. CANTAB Machine



Figure 2. Marmoset in transport box working on the reversal learning task



Figure 3. Marmoset working in the WGTA version of the test.







	SD1/SR1	SR2/SD2 or SD3/SR3	
Year 1			
Year 2			

Figure 4. Stimuli used in Simple Discriminations (SD) and Simple Reversals (SR) in year 1 and year 2.

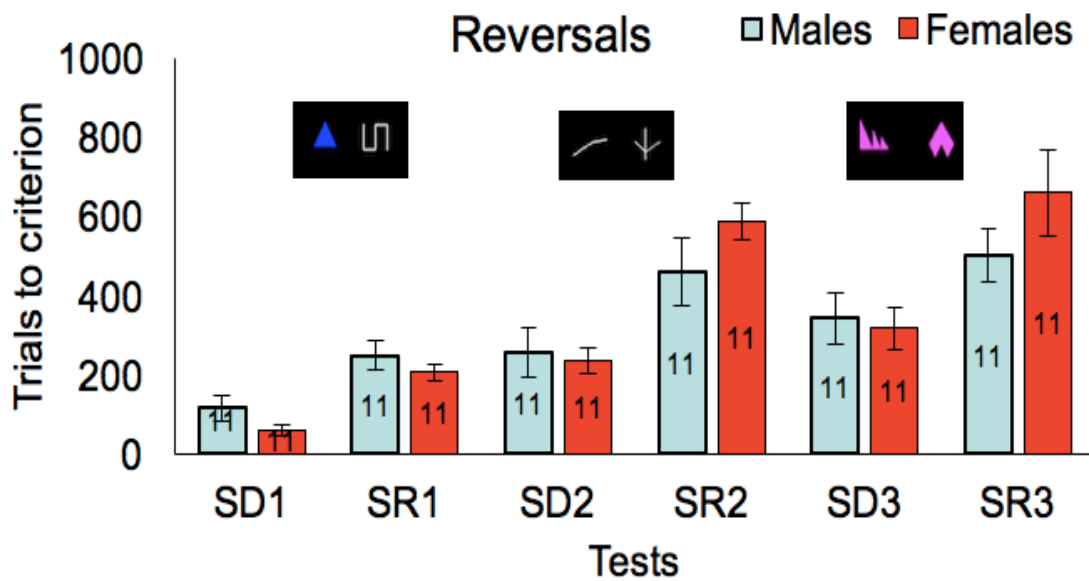


Figure 5. Trials to criterion (TTC) as a function of sex and test for marmosets tested in Year 1 (n=22).

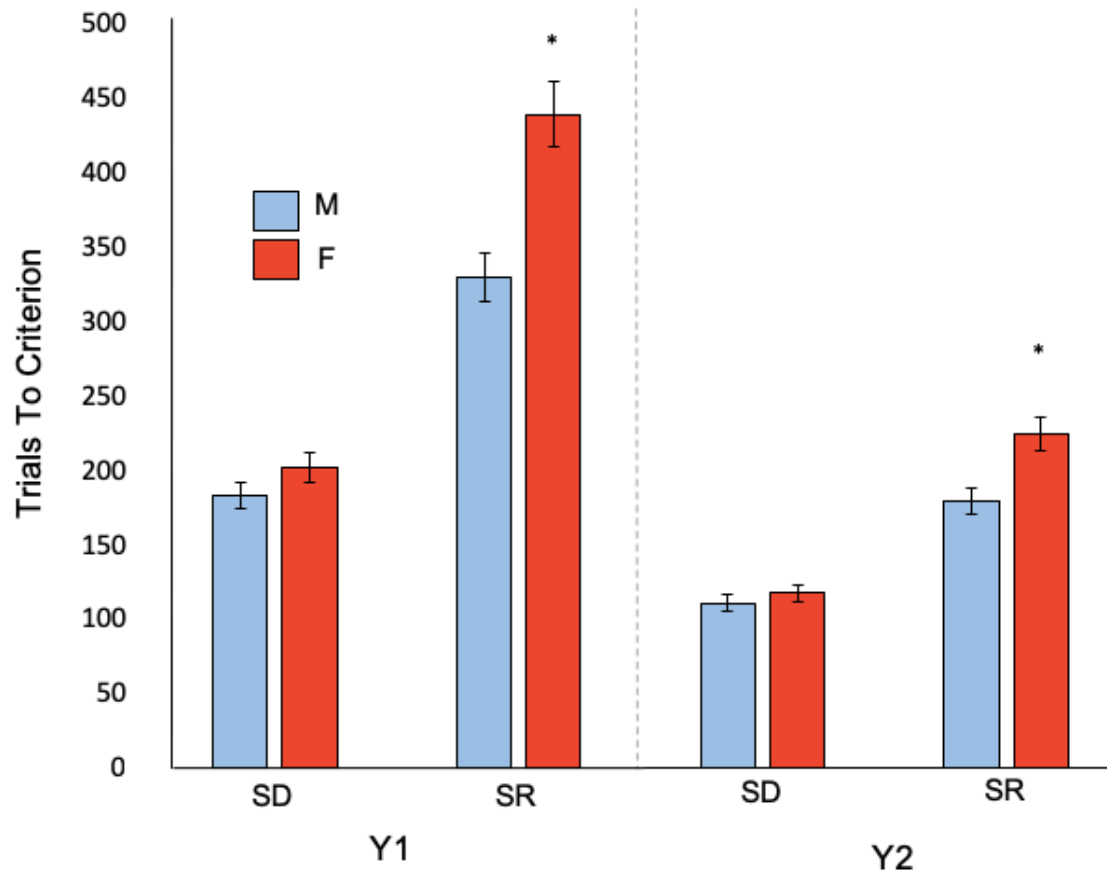


Figure 6. TTC as a function of test type for males and females Year 1 and Year 2. SD: simple discriminations; SR: simple reversals. * $p < .05$.

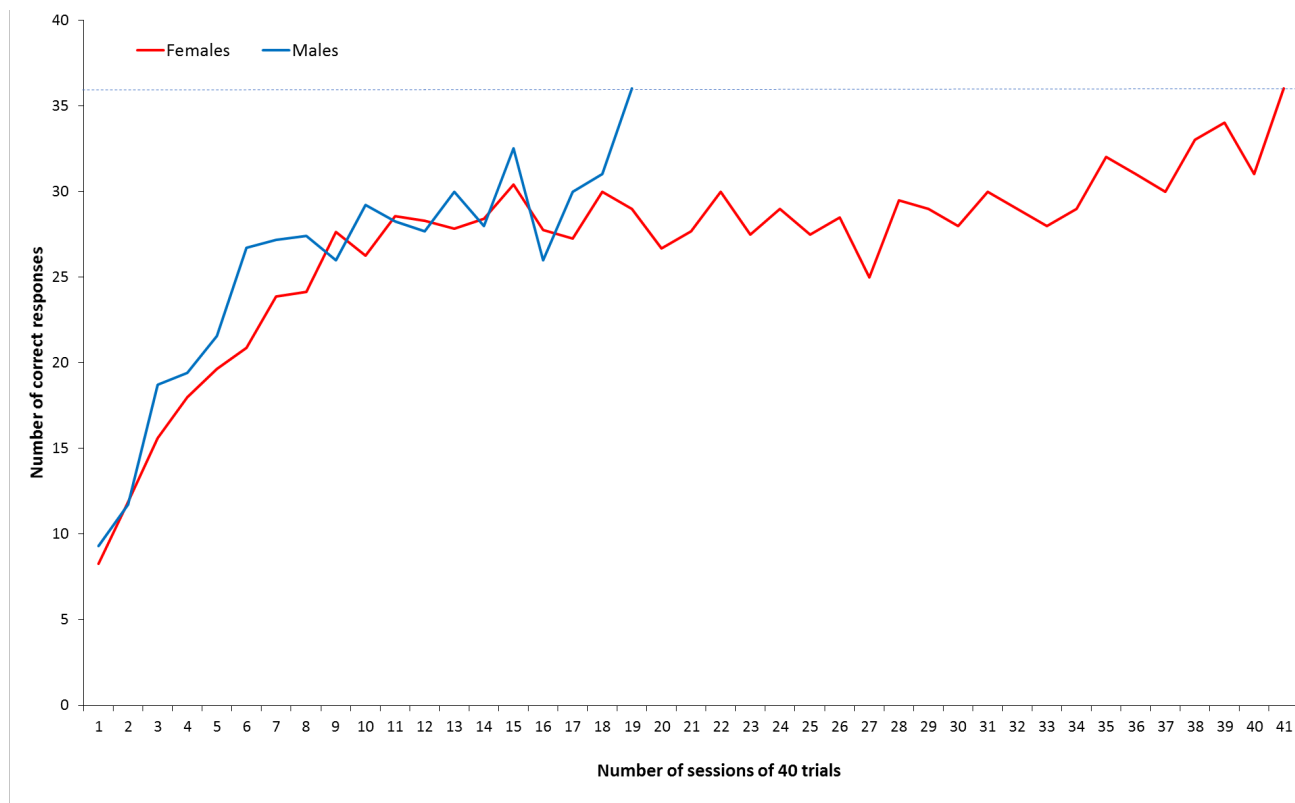


Figure 7. Number of correct responses as a function of number of sessions of 40 trials in male and female marmosets (n=16) in the SR3 reversal. The dotted line marks the 90% correct criterion (36/40 responses).

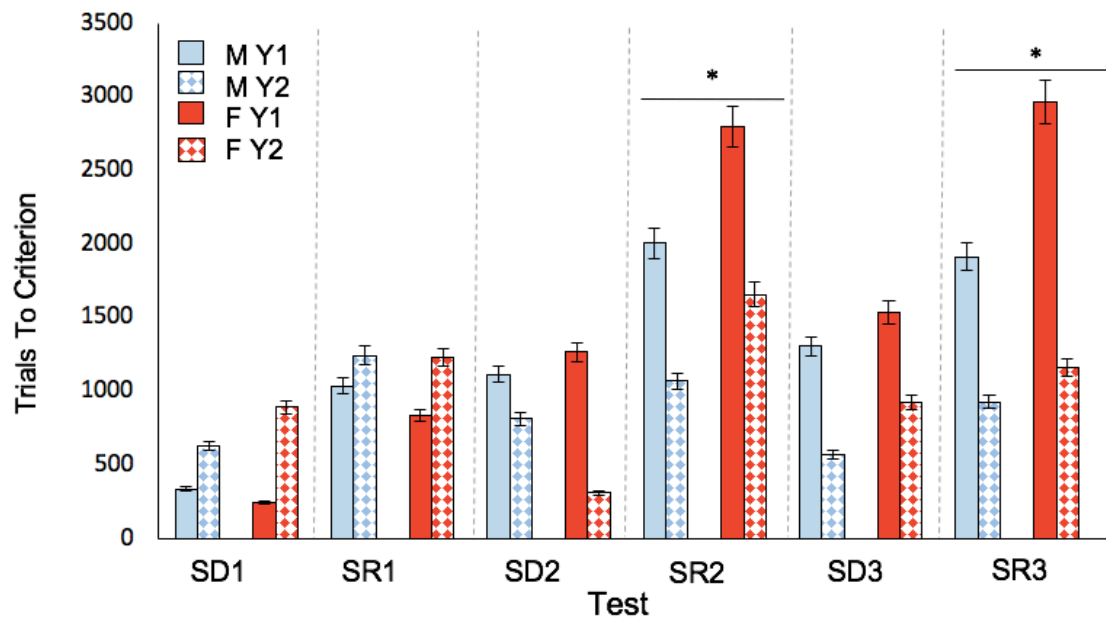
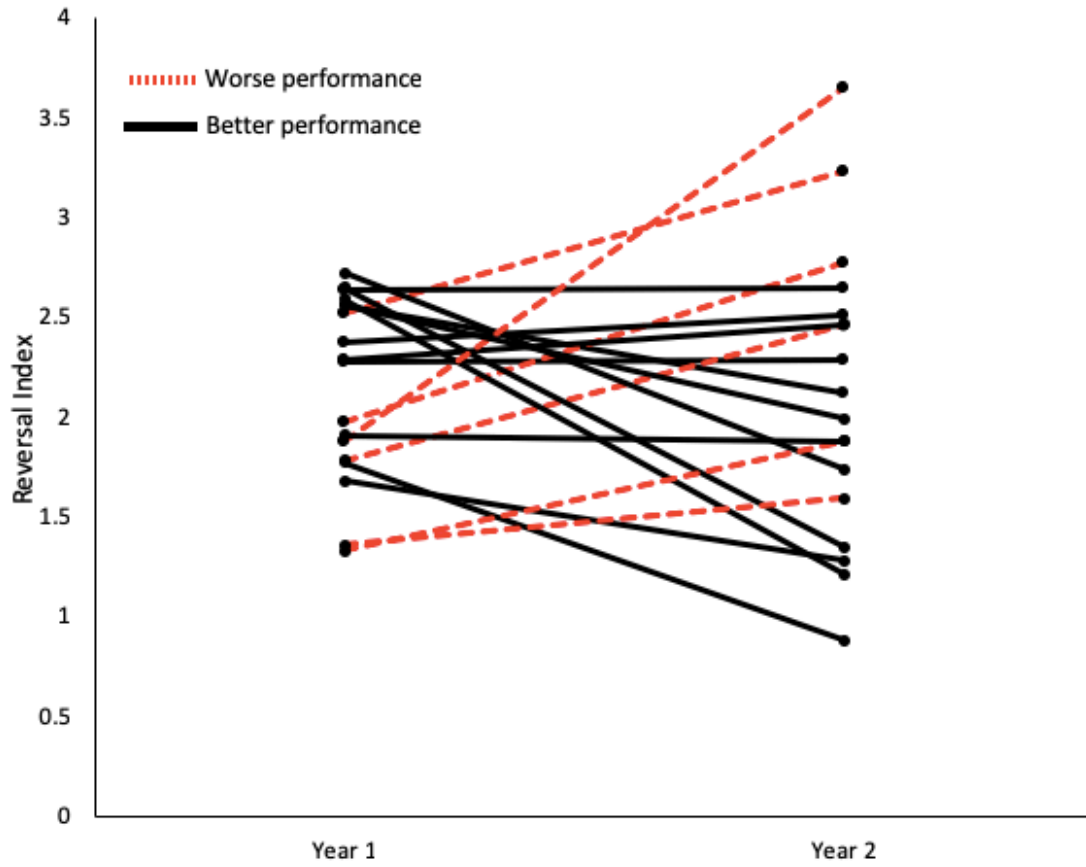


Figure 8. TTC as a function of test for males in females in Year 1 and Year 2 * $p < .05$.



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